REMARKS

I. Preliminary Remarks

Applicants gratefully acknowledge the Examiner's withdrawal of the 35 USC §112, second paragraph rejection, and the withdrawal of the nonstatutory obviousness-type double patenting rejection based upon the acceptance of the terminal disclaimer over U.S. Patent No. 5,387,676. Applicants also appreciatively acknowledge Examiner's finding that Claims 31-35 and 53-55 are in condition for allowance.

II. 35 USC 112, First Paragraph Rejection

Rejoined process claims 39 and 40 stand rejected under 35 USC 112, first paragraph, "as failing to comply with the enablement requirement." [Office Action dated October 4, 2006 ("Office Action"), page 3.] The Office Action goes on to state in the middle of page 4:

> [T]o determine whether the MN antisense construct comprising a complementary sequence of SEQ ID NO: 5 would effectively inhibit the expression of the MN gene in a human subject would require undue experimentation. The claimed invention must be enabled at the time of the effective filing date, which antedates to the year of 1992 when the antisense therapeutics as well as DNA-based therapeutics as a whole were nascent and the clinical data proving the efficacy of such therapeutics were meager.

Applicants respectfully traverse the rejection, first pointing out that an analogous rejection of methods of treating precancer/cancer with MN antisense oligonucleotides in the parent application [U.S. Serial No. 08/260,190] was overturned on appeal to the PTO's Board of Patent Appeals and Interferences, which found the claims enabled in a Decision dated July 23, 2003 [Appeal No. 2001-1970]. Applicants respectfully point out that the case for the enablement of the subject claims, which concern such treatment methods using MN antisense constructs, rather than simply MN antisense olgonucleotides as in the parent application, is ever stronger. The Board's July 23, 2003 Decision holding the claims of the parent application to be enabled should apply even more strongly to the subject Claims 39 and 40. Applicants respectfully provide the case for enablement below, as they did in the parent application.

Applicants respectfully submit that enablement sufficient for the skilled worker to make and use the claimed invention is found in the Specification and articles incorporated by reference, in combination with conventional knowledge in the art. Applicants also respectfully argue that the PTO's initial burden of proof to challenge the presumptively enabling specification has not been met.

The accompanying Appendix I with a 1.132 Declaration from one in skill in the art, submitted as evidence during the prosecution of the parent application 08/260,190 (now U.S. Patent No. 6,774,117), supports Applicants' assertion that the in vitro inhibition of cellular growth and decrease of MN expression mediated by MN antisense constructs, in view of the scientific literature at the priority date of the instant application, is reasonably predictive of the efficacy of MN antisense constructs in treating MN-expressing cancer in humans.

Regarding the Examiner's case for lack of enablement, the Manual of Patent Examining Procedures (MPEP) § 2164.04 entitled "Burden on the Examiner Under the Enablement Requirement" directs that the initial burden of proof to challenge a presumptively enabling disclosure is upon the Examiner. The patent case law, as well as the MPEP, makes clear that in accordance with case law, statements in a patent specification relied upon for enabling support that correspond in scope to a claimed invention "*must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of" those statements. [In re Marzocchi, 169 USPQ 367, 369 (CCPA 1971); italicized emphasis in the original; underlined emphasis added; see also, In re Brana, 34 USPQ2d 1437 (Fed. Cir. 1995).]

A. Enablement in the Specification, Articles Incorporated by Reference, and Conventional Art

The MN gene and MN protein are considered to be a putative oncogene and oncoprotein, respectively. [Specification, page 9, lines 6-8 and page 1, lines 17-19.] Studies have demonstrated the oncogenic activity of the MN gene. Transfection of non-tumorigenic cells with a plasmid containing MN cDNA confers tumorigenic properties upon those previously non-tumorigenic cell lines. [Specification, page 64, line 5 to page 65, line 8; Example 15, page 133, line 3 to page 137, line 2; and Example 16, page 137, line 3 to page 140, line 23.][1]

Applicants expected that the MN gene being an oncogene, would have anti-tumor antisense activity as shown for other oncogenes, such as, for the HER-2/neu/c-erbB-2, c-myc, c-

1. For example, the subject specification, at pages 63, line 18 to page 67, line 9 and at page 133, line 3 to page 141, line 23, describes the relationship between MN expression and cell growth. When non-tumorigenic (NIH 3T3) cells were stably transfected with MN cDNA, the "cells acquired features associated with a transformed phenotype: altered morphology, increased saturation density, proliferative advantages in serum-reduced media, enhanced DNA synthesis and capacity for anchorage-independent growth." [Specification, page 64, lines 5-13; and Example 15, page 133, line 3 to page 137, line 2.] Example 16 (page 137, line 3 to page 140, line 23) shows that those NIH 3T3 transfectants that constitutively express MN protein had accelerated progression through the G1 phase, reduced cell size, "the loss of capacity for growth arrest under inappropriate conditions . . . ", and displayed "a decreased sensitivity to the DNA damaging drug mitomycin C." [Specification, page 6, lines 13-20.]

myb, Bcl-2 and N-ras oncogenes. The Applicants tested MN for such anti-tumor antisense activity. The specification at page 65, line 18 to page 67, line 9 describes experiments wherein a tumorigenic human cell line (CGL3 cells) was transfected with a plasmid containing "antisense" MN cDNA, and the opposite effect occurred than that of transfecting non-tumorigenic cells with plasmids containing "sense" MN cDNA. Compared to non-transfected cells, the antisense-transfected tumorigenic cells formed smaller colonies and had a very much lowered proliferation rate. The specification also showed that the MN gene expression of MN-expressing human cervical cancer cells (HeLa cell line) was decreased in vitro when MN antisense nucleotides were added to the media. [Example 10, page 118, line 20 to page 120, line 12; and Figure 3, described at page 24, lines 12-17.]

Specification

Support for the claimed invention can be found in the specification at least at page 15, lines 3-14; at page 24, lines 12-17 describing Figure 3; at page 48, lines 14-26; at page 53, line 18 to page 54, line 20; at page 63, line 18 to page 67, line 9; at page 92, line 1 to page 94, line 11; in Example 10 at pages 118-120; and in Example 13 at pages 123-132. Further indirect support can be found in Example 15 at page 133, line 3

to page 137, line 2; and in Example 16, page 137, line 3 to page 141, line 23. Particular support for the therapeutic methods of Claims 39 and 40 (using MN antisense constructs) is provided by the experiments reported at page 65, line 19 to page 67, line 9, showing that MN antisense constructs caused tumorigenic human MN-expressing hybrid cells -- CGL3 cells -- to form smaller colonies and have a very much lowered proliferation rate compared to control CGL3 cells, and to stop expressing MN protein for a period.

Inhibition of MN expression with specific antisense oligodeoxynucleotides (ODNs) -- SEQ ID NOS: 3 and 4 -- was also shown in Example 10 (at page 118, line 20 to page 120, line 12) to inhibit MN gene expression and provides an in vitro screening method to detect MN antisense nucleic acids that would be expected to be active. Example 13 provides a routine immunological method to determine if a preneoplastic/neoplastic disease is associated with abnormal MN gene expression with an ATCC-deposited MN-specific monoclonal antibody.

Further, the specification at pages 24 (Figure 3), 48, 65-67, and 118-120 provides evidence that the treatment of abnormally expressing MN cells with MN antisense nucleic acids, including those delivered via constructs, would be expected to reduce the expression of MN in such cells, to lower the proliferation rate of such cells, and reduce the size of

colonies. That evidence includes the experiments outlined in Sections 3(a) and 4-6 of the 1.132 Declaration of Dr. Gruenert. Those experiments in the context of the specification support Claim 39 (a method of blocking in vivo expression of the MN gene in a human by administering an MN antisense construct); and Claim 40 (a method of treating neoplastic disease in a human by administering an MN antisense construct). Because therapeutic methods using antisense constructs overcome potential drawbacks of those using naked DNA (e.g., no mechanism for persistence or stability of the antisense DNA), the claimed methods of Claims 39 and 40 would potentially work better than those using only naked MN antisense DNA.

Articles Incorporated by Reference. Enablement for the therapeutic methods of claims 39 and 40 is also supported by the articles on antisense therapy at page 92, line 1 to page 93, line 18 that were incorporated by reference into the specification. [See page 143, lines 4-5.] Each of the 20 references teaches aspects of how to design, make, deliver, and evaluate the efficacy of antisense oligonucleotides.

Conventional Art, Scope of Claims, Routine Experimentation

The Office Action states at the bottom of page 5:

> [I]t is clear that based on the state of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the method drawn to blocking the MN gene expression and treating neoplastic disease in humans comprising administering the MN antisense construct of claim 31 would be used without undue experimentation.

Applicants respectfully disagree and direct attention to the statement in MPEP 2164.01 Section entitled "Test of Enablement": "A patent need not teach, and preferably omits, what is well known in the art." Also, as the Patent and Trademark Office Board of Appeals and Interference [the "Board"] affirmed in Ex parte Forman, 230 USPQ 546 at 547 (PTO Bd. App. & Interf. 1986) the "test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine. . . ."

Routine experimentation is not considered undue. Applicants respectfully submit that only routine experimentation is involved in screening for therapeutically effective MN antisense nucleic acids in accordance with the procedure of Example 10, and in the immunohistochemical staining method described in Example 13 to determine whether a preneoplastic/neoplastic disease is associated with abnormal MN gene expression. Further, Applicants respectfully submit that only routine experimentation is required to choose an appropriate vector, standard mode of administration or dosage

amount analogous to what was used for other antisense constructs in in vivo animal model and clinical studies. That such experimentation is considered routine, and not undue, by those of skill in the art is supported by the 1.132 Declaration of Dr. Gruenert in accompanying Appendix I.

Moreover, counter to the Office Action's above assertion, a Declaration by one of skill in the antisense art — Dr. Gruenert, Co-Director of the University of California at San Francisco (UCSF) Gene Therapy Core Center — was submitted with the response sent to the PTO in the parent application 08/260,190 (now U.S. Patent No. 6,774,117) on July 17, 1997 and accompanies this response as Appendix I. Dr. Gruenert declared in Section 3(b) that "the in vitro screening studies shown [in the Specification] would permit workers of skill in the art to select antisense MN oligonucleotides which would be therapeutically useful." [Emphasis added.] In Sections 7 and 8, he detailed the reasoning for that statement.

Dr. Gruenert declares in Sections 7 and 8:

> 7. The Specification also described a screening procedure using HeLa cells in vitro for selecting therapeutically useful antisense MN oligonucleotides. Example 10, described at pages 118-120, and Figure 3, show that MN antisense oligonucleotides suppressed MN gene expression in those human cancer cells. . . .
>
> 8. I further declare that the published literature taught routine methods

> for designing, making, delivering, and evaluating oligonucleotides . . . for successful in vivo use. Thus, I declare that I believe that a worker of ordinary skill would be able to use the routine screening system described in Example 10 to select therapeutically useful MN antisense oligonucleotides. Based on the studies reported in the specification, it can be reasonably assumed that an MN antisense oligonucleotide which inhibits expression of MN protein in MN expressing tumorigenic cell lines, such as HeLa or CGL3 cell lines, would be therapeutically useful.

Applicants respectfully point out that Dr. Gruenert refers in his Declaration to published literature at or before the priority date for the claimed invention, that is, in 1992.

Methods Using Nucleic Acid Constructs Versus Naked DNA

Further, Applicants respectfully argue that the claimed methods using MN nucleic acid constructs could be expected by one of skill in the art to work better for antisense therapeutics than methods using isolated MN nucleic acids. For example, the Yokoyama et al. article cited at page 100 of the instant specification and incorporated by reference [Yokoyama et al., "Transcriptional Regulation of c-myc Protooncogene by Antisense RNA"; pp. 35-51, Prospects for Antisense Nucleic Acid Therapy of Cancer and AIDS, (Wiley-Liss, Inc., New York, NY, USA; 1991)] extensively discusses the design and use of *c-myc* antisense constructs for constitutive inhibition of *c-myc* gene

expression in human cells, compared with the transient inhibition by antisense c-*myc* oligonucleotides reported earlier by Wickstrom et al. [*In Vitro* Cell. Dev. Biol., 24: 297-362, 1989].

Pioneering Inventions

The case law is clear that pioneer inventions are entitled to broad claim coverage.[2] The purpose recited in the U.S. Constitution for granting patents is "to promote the progress of science and the useful arts by securing for limited times to . . . inventors the exclusive right to their respective . . . discoveries." Applicants respectfully submit that the goal of the Constitution quoted above would not be served by refusing pioneer inventors claims to their new contribution to cancer treatments.

The Court of Customs and Patent Appeals (CCPA), predecessor court to the Federal Circuit,[3] stated in In re Goffe, 191 USPQ 429 at 431 (CCPA 1976):

> [T]o provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall

2. A basic patent on a pioneering invention is entitled to be interpreted broadly. Texas Instruments, Inc. v. United States ITC, 231 USPQ 833 (Fed. Cir. 1986).

3. The holdings of the CCPA were adopted as precedent by the Federal Circuit in South Corp. v. United States, 215 USPQ 657 (Fed. Cir. 1982).

> limit his claims to what he has found will work. . . . would not serve the constitutional purpose of promoting progress in the useful arts.

The CCPA further pointed out in In re Hogan and Banks, 194 USPQ 527 at 537 (CCPA 1977):

> As pioneers, . . . they would deserve broad claims to the broad concept. What were once referred to as 'basic inventions' have led to 'basic patents,' which amounted to real incentives, not only to invention and its disclosure, but to its prompt, early disclosure. . . .
>
> . . . To demand such restriction is merely to state a policy against broad protection for pioneer inventions, a policy both shortsighted and unsound from the standpoint of promoting progress in the useful arts, the constitutional purpose of the patent laws.

In In re Fisher, 166 USPQ 28 at 24 (CCPA 1970), the CCPA considered it "apparent" that a pioneering invention should be able to dominate the future patentable inventions of others where those inventions were based in some way on his/her teachings, that is, where "the improvement was made possible by his work." The recognition by the Applicants that MN antisense nucleic acids are therapeutically useful for the many preneoplastic/neoplastic diseases associated with abnormal MN gene expression, provides a benefit to the public as another

option for cancer treatment. It is the contribution of that knowledge that is the invention.

Applicants respectfully submit that once an appropriate antisense target is identified, it is conventional knowledge to use the same modes of administration, dosage ranges as used therapeutically for other antisense nucleic acids. The 1.132 Declaration of Dr. Gruenert of Appendix I supports that statement. He declared in Section 8 "that the published literature taught routine methods for designing, making, delivering, and evaluating oligonucleotides for successful in vivo use."

What is important about the claimed invention is the discovery by the Applicants that MN nucleic acids complementary to the MN cDNA (SEQ ID NOS: 1 and 5) are useful for antisense therapy of preneoplastic/neoplastic diseases associated with abnormal MN gene expression. Once the Applicants identified MN as a putative oncogene and that MN's antisense nucleic acids exhibited antisense activity, one of skill in the art could adapt the procedures and dosage ranges used successfully with structurally similar antisense nucleic acids in in vivo studies, **in view of only a small amount of therapeutic activity needing to be enabled to meet the patentability standard**.

Summary: Applicants respectfully conclude that the specification is enabling of the claimed invention in view of its disclosure, the 20 references incorporated by reference, and by what was known conventionally in the art. Applicants respectfully conclude that only routine experimentation is required:

(1) to select therapeutically effective MN antisense nucleic acids (e.g. by the in vitro, screening method of Example 10) and suitable delivery vectors;

(2) to determine if a preneoplastic/neoplastic disease is associated with abnormal MN gene expression in a human (e.g., by the immunohistochemistry method of Example 13 with the MN-specific M75 monoclonal, the hybridoma for which is deposited at the ATCC); and

(3) to adapt standard modes of administration and dosage ranges of antisense constructs from successful in vivo studies with structurally similar antisense nucleic acids.

B. PTO's Initial Burden of Proof to Challenge Presumptively Enabling Specification Not Met

Applicants respectfully submit that the PTO has not established a prima facie case of nonenablement. The Office Action argues that the specification is not enabling because of the meagerness of clinical data proving the efficacy of

antisense therapeutics as of 1992; the little guidance provided in the specification; the absence of working examples in humans; and the unpredictability of the art of antisense therapeutics [Office Action, middle of page 4 to top of page 5.] In support of the unpredictability of the antisense art and the lack of in vivo/in vitro correlation, the Office Action cites Patil et al. [The AAPS Journal, 7(1): E61-E77, 2005]. Applicants respectfully counter each of those arguments below under the respective headings, and then demonstrate why the cited Patil et al. reference does not cast doubt on statements in the specification relied upon for enabling support.

Clinical Data as of 1992

At the bottom of page 5 the Office Action states that:

> based on the state of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the method drawn to blocking the MN gene expression and treating neoplastic diseases in humans comprising administering the MN antisense construct of claim 31 would be used without undue experimentation.

However, clinical trials with other antisense nucleic acids are evidence that one of skill in the art would reasonably expect MN antisense nucleic acids to work in vivo to treat humans, and there are conventional methods available in the art to administer and deliver antisense nucleic acids to their targets

in vivo. MPEP § 2107.02 emphasizes by underlining that there is a presumption that the initiation of human clinical trials for a therapeutic process establishes "that the subject matter of that [clinical] trial is reasonably predictive of having the asserted therapeutic utility." [Emphasis in original.] Applicants respectfully submit that it is only a common sense inference therefrom that in vivo animal studies leading up to the initiation of such human clinical trials are reasonably predictive of a human therapeutic utility. Further, the initiation of human clinical trials with antisense nucleic acids provide evidence that there are modes of administration and dosage amounts that are accepted in the art for antisense therapy as declared by Dr. Gruenert in the 1.132 Declaration of Appendix I.

Guidance in the Specification

The Office Action states at the top of page 5 that "the instant specification does not provide any . . . guidance/direction as to how to practice the instantly claimed invention *in vivo* in humans." Applicants respectfully point out that the MPEP states in §2164.01(c) entitled "How to Use the Claimed Invention":

> If a statement of utility in the specification contains within it a connotation of how to use, and/or the art

> recognizes that standard modes of administration are known and contemplated, 35 U.S.C. 112, is satisfied. *In re Johnson* . . . . 127 USPQ 216, 219 (CCPA 1960); *In re Hitchings*, . . . 144 USPQ 637, 643 (CCPA 1965). See also *In re Brana* . . . 34 USPQ2d 1437, 1441 (Fed. Cir. 1993).
>
> For example, it is not necessary to specify the dosage or method of use if it is known to one skilled in the art that such information could be obtained without undue experimentation. If one skilled in the art, based on knowledge of compounds having similar physiological or biological activity, would be able to discern an appropriate dosage or method of use without undue experimentation, this would be sufficient to satisfy 35 U.S.C. 112.

[Emphasis added.] Applicants respectfully submit that once an antisense nucleic acid target has been identified, the structural similarity of nucleic acids renders prior art methods of designing, making, delivering, and evaluating other antisense nucleic acids to be expected by one of the skill in the art to be equally useful for newly identified antisense nucleic acids. In regard to "how to use" and "standard modes of administration" being known, Dr. Gruenert's Declaration of Appendix I states in paragraph 8: "I further declare that the published literature taught routine methods for designing, making, delivering and evaluating oligonucleotides . . . for in vivo use." [Emphasis added.] Those routine methods are sufficient for enabling the small amount of therapeutic utility shown by earlier antisense nucleic acids.

Applicants respectfully point out: "A patent need not teach, and preferably omits, what is well known in the art." [Spectra-Physics, Inc. v. Coherent, Inc., 3 USPQ2d 1737, 1743 (Fed. Cir. 1987).] The case of In re Hitchings, Elion and Goodman, 144 USPQ 637 (CCPA 1965) concerned an application that did not contain information concerning "methods or manner of administration, dosages, etc." for chemotherapeutic compounds. The CCPA stated in that case that

> [s]uch a lack, however, does not per se render the disclosure inadequate under section 112. All the statute requires is that the disclosure be one which will "enable any person skilled in the art to which it pertains, or, with which it is most nearly connected," to make and use the invention. Thus, where the manner of using a claimed compound is obvious to one of ordinary skill in the particular art, even though the specification is utterly barren of any express teaching of how to use, this court has found compliance with section 112.

Applicants respectfully submit that the art at the claimed priority date as represented by the articles incorporated by reference provide examples of certain standard methods of using antisense nucleic acids against neoplastic and other diseases in humans, and that such methods are known to those of skill in the art. Applicants respectfully submit that it would be apparent to one skilled in the art that the MN antisense nucleic acids could be used in the same manner as

other antisense nucleic acids, particularly those of other oncogenes analogous to the MN oncogene.

Concerning undue experimentation, the Patent and Trademark Office Board of Patent Appeals and Interferences stated in Ex parte Forman, 230 USPQ 546 at 547 (PTO Bd. App. & Interf. 1986) that the "test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine. . . ." Applicants respectfully submit that in view of the Declaration of Dr. Gruenert and the prior art references cited in the specification concerning the use of antisense nucleic acids, that analogous modes of vector design, administration, formulations and dosages could be employed with MN-specific antisense nucleic acids. Applicants respectfully submit that experimentation involved in adjusting such methods would be routine, and thus in accordance with Ex parte Forman, supra, would not be undue.

In Vitro/In Vivo Correlation and Working Examples

The Office Action refers at page 5 to there being no in vivo working examples of the claimed methods in humans. Applicants respectfully point out that there at the time of filing an application, an applicant need not have any examples to provide enablement. As the Federal Circuit has stated:

> The first paragraph of § 112 requires nothing more than *objective* enablement. *In re Marzocchi*, . . . , 169 USPQ 367, 369 (CCPA 1971). How such a teaching is set forth either by the use of illustrative examples or by broad terminology, is irrelevant.

[In re Vaeck, 20 USPQ2d 1438 at 1445 (Fed. Cir. 1991); emphasis added.]

However, MPEP § 2164.02, which concerns compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, points out that an in vivo "working example" can arise from an in vitro example if one of skill in the art "would accept the model as reasonably correlating to the condition."

MPEP § 2164.02 entitled "Working Example" states:

> CORRELATION: *IN VITRO/IN VIVO*
>
> The issue of "correlation" is related to the issue of the presence or absence of working examples. "Correlation" as used herein refers to the relationship between *in vitro* or *in vivo* animal model assays and a disclosed or a claimed method of use. An *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention. If there is no correlation, then examples do not constitute "working examples." In this regard, the issue of "correlation" is also dependent on the state of the prior art. In other words, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and

> decide whether one skilled in the art would accept the model as reasonably correlating to the condition. *In re Brana*, . . . 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications).

[Emphasis added.]

In Vitro/In Vivo Correlation -- Dr. Gruenert's Declaration of Appendix I

Dr. Gruenert, as one skilled in the art, attests to the correlation between the in vitro examples in the specification and in vivo therapeutic utility in his 1.132 Declaration of Appendix I. For example, in paragraph 3(a), he declares:

> that the in vitro results shown in the subject specification, for example at pages 65-67, reasonably predict in vivo therapeutic efficacy of MN antisense oligonucleotides for the following reasons. First, there is a strong association of MN gene expression with tumorigenesis. Second, transfection experiments with MN sense and antisense constructs, in non-tumorigenic and tumorigenic cell lines, respectively, show that MN sense constructs cause non-tumorigenic cells to exhibit a transformed phenotype, whereas the antisense constructs cause the tumorigenic cells to have a very much lowered proliferation rate and to form smaller colonies than controls. Third, prior studies show that the in vitro effects observed in studies of other, structurally similar oligonucleotides, correlate with in vivo therapeutic effects.

[Emphasis added.] Applicants respectfully point out that the quote from Dr. Gruenert's Declaration is not just based on representative prior art studies but also on factual evidence as demonstrated in the above quotation.

Dr. Gruenert makes similar statements throughout the Declaration and also states in Section 8: "I further declare that the published literature taught routine methods for designing, making, delivering and evaluating oligonucleotides . . . for successful in vivo use." [Emphasis added.] Dr. Gruenert's Declaration, as exemplified by the above quotes, attests to the correlation between the in vitro examples provided in the specification and the in vivo therapeutic use of MN antisense nucleic acids in humans.

Applicants respectfully point out that the tumorgenic CGL3 cells that were the subject of the MN antisense transfection experiments are human cells [Specification, page 21, line 26; page 20, lines 1-17; and page 17, lines 16-17], as are the HeLa cells that are the subject of the in vitro method of screening for antisense activity of Example 10 (page 118, line 20 to page 120, line 12).

Dr. Gruenert then declares in Sections 5-6:

> (c) Conversely, the specification at pages 65-67 described studies in which a plasmid containing an antisense MN cDNA had an opposite effect in a tumorigenic cell line, CGL3. Compared to non-transfected

cells, the antisense-transfected tumorigenic cells formed smaller colonies and had a very much lower proliferation rate. Thus, I declare that the results from the transfection experiments reported in the specification with sense and antisense nucleic acids in non-tumorigenic and tumorigenic cell lines shows that MN expression affects cell growth and is strongly correlated with tumorigenesis.
(d) The studies of CGL1 cells, 3T3 cells, and CGL3 cells each support the contention that MN is an oncogene that can regulate the abnormal growth of cancer cells. Thus, I declare that the above-described studies, in combination with the immunological studies described above in paragraph 4 provide a strong basis for expecting that inhibiting MN expression using antisense oligonucleotides would inhibit the growth of MN expressing tumor cells.

6. I declare **that I am aware of the published literature at the time of filing the application,** and that this literature generally taught the relationship between antisense oligonucleotide structure and efficacy of in vivo inhibition of the expression of any gene whose DNA sequence is known. [See for example, Zamecnick, P.D., Prospects for Antisense Nucleic Acid Therapy of Cancer and AIDS, Wiley-Liss, Inc., New York, NY, USA; (1991), pages 1-6; cited on page 92 of the Specification.] The work of Mirabelli et al., Anti-Cancer Drug Design, 6: 647-661 (1991), described some of the studies which demonstrated efficacy of antisense ODNs structurally similar to those of the present invention inhibiting transcription of the oncogenes, c-myc, c-myb, BCL-2 and N-ras. Further, studies of Kitajima et al., Science 258:1792-1795 (1992), Ratajczak et al., Proc. Nat. Acad. Sci. 89:11823-11827 (1992), Chiasson et al., Eur. J. Pharm.-Mol. Pharm. Section 227:451-453 (1992) and Wickstrom et al., Cancer Res. 52:6741-6745 (1992) each support the use of

> antisense ODNs of similar structure to MN antisense ODNs in treating diseases in vivo. Zamecnick, Ratajczak et al., Chiasson et al., and Wickstrom et al. were cited in the Specification or in the Information Disclosure Statement filed for this application. A copy of Mirabelli et al. is appended to this declaration. Because of the strong correlation between MN expression and tumorigenesis, and because of the structural similarity between MN antisense oligonucleotides and oligonucleotides shown in the above-identified references to inhibit expression of other cancer genes and cellular proliferation in vivo, I declare that the in vitro inhibition of cellular growth by MN antisense nucleic acids as shown at pages 65-67 is reasonably predictive of the efficacy of MN antisense oligonucleotides in treating MN-expressing human cancer.

[Emphasis added.] Applicants respectfully emphasize that Dr. Gruenert refers to the published literature at the effective filing date of the subject application, and citing 1991 and 1992 references. The effective filing date for the instant application is in 1992. Applicants respectfully conclude that the Examiner must consider the assessment of Dr. Gruenert, one of skill in the art who based his conclusions on particular studies concerning the MN oncogene and on the literature at the claimed priority date concerning in vivo efficacy of structurally similar antisense nucleic acids from analogous oncogenes.

Patil et al. and Unpredictability of the Art

At page 4, the Office Action cites Patil et al. as teaching the unpredictability of DNA-based drugs:

> The innate ability of DNA-based drugs to be internalized by target cells is minimal under normal circumstances. In addition, poor biological stability and a short half-life result in unpredictable pharmacokinetics. Furthermore, DNA molecules that do manage to enter the cell are subsequently subjected to intracellular degradation along with stringently restricted nuclear access.

[Patil et al., The AAPS Journal, 7: E61-E77, 2005; at page E62, 1st column.] However, the same Patil article goes on to review different means to overcome challenges of DNA-based drug therapy, and describes the most promising solution to the problems of DNA-based drugs: delivery systems, including plasmid or viral DNA delivery vectors. [For example, see sections in Patil et al. entitled "Plasmids" (pages E62-E65) and "Vector-Assisted Delivery Systems (pages E68-E69), as well as Figure 1 (5)]: "The use of DNA delivery systems has not only improved the pharmacokinetics of DNA-based therapeutics but has also achieved efficient targeted introduction of these molecules into desired tissues." (Patil et al., page E62, 2nd column; emphasis added.) "[C]ellular delivery of DNA assisted by delivery systems has matured from a laboratory science into a methodology suitable for use in clinical trials of DNA-drug

candidates. . . ." [Id., page E68, bottom of 2nd column; emphasis added.] Therefore, Patil et al. can be read to confirm that methods using the MN antisense constructs of Claim 31 would be expected by the skilled artisan to be sufficiently predictable to be "suitable for use in clinical trials of DNA-drug candidates. . . ." [Id.]

In re Vaeck

In the middle of page 5 of the Office Action, the Examiner cites In re Vaeck [947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991)], wherein the Court ruled that a rejection under 35 USC 112, first paragraph for lack of enablement was appropriate given the relatively incomplete understanding of the biotechnological field involved. However, the patent application in In re Vaeck related to a genetically engineered cyanobacterium capable of expressing an insecticidal protein, all but one of the claims not being limited to any particular genus or species of host cyanobacterium. The broad claims were rejected, as "the cyanobacteria are a diverse and relatively poorly studied group of organisms, comprising some 150 different genera. . . .". That rejection clearly does not apply to the biotechnological field of Claims 39 and 40 of the instant application, as the sole host species (human) is well-studied.

SUMMARY

Applicants respectfully summarize, first pointing out that the burden is first upon the Patent and Trademark Office (PTO) to show that there is "reason to doubt the objective truth of the statements contained . . . [in the instant specification] which must be relied upon for enabling support." [In re Marzocchi, 169 USPQ 367 (CCPA 1971), and In re Brana, 34 USPQ2d 1437 (Fed. Cir. 1995).] Applicants respectfully conclude that in accordance with MPEP § 2164.01(c) and Dr. Gruenert's Declaration, routine methods for designing, making, delivering and evaluating antisense nucleic acids for in vivo use are available in the prior art. The Specification's disclosure in view of conventional knowledge enables one of skill in the art to make and use the claimed methods without undue experimentation, at least for the small degree of antisense therapeutic utility required for patentability.

In accordance with MPEP § 2164.02 and Dr. Gruenert's Declaration, one of skill in the art is shown to accept an in vitro model as reasonably correlating with in vivo activity, thereby providing "working examples" [MPEP § 2164.02] and a routine method to select therapeutically effective MN antisense nucleic acids complementary to MN cDNA. Example 13 has been shown to provide a routine method to identify target

preneoplastic/neoplastic diseases as those associated with abnormal MN gene expression.

Applicants in discussing the cited Patil et al. reference respectfully emphasize that it is very clear in the case law and directed by the MPEP that clinical testing is not necessary to establish efficacy for an invention related to treating human disorders. [In re Brana, 34 USPQ2d 1436, 1442 (Fed. Cir. 1995); MPEP § 2107.02(d).] The Federal Circuit in In re Brana, 34 USPQ2d 1436 at 1442 (Fed. Cir. 1995) emphasized that clinical testing for methods of treating cancer in humans was not required "for obtaining a patent."

Further, "optimality is not required for a valid patent." [Atlas Power Co. v. E. I. du Pont de Nemours & Co., 224 USPQ 409, 414 (Fed. Cir. 1984); and Phillips Petroleum Co. v. U.S. Steel Corp., 6 USPQ 1065, 1105 (D. Del. 1987), aff'd, 9 USPQ 1461 (Fed. Cir. 1989) ("[T]he utility need not be commercially useful [or] marketable.").] "A showing of some utility is all that is required for patentability." [Cameo Industries Inc. v. Lousiana Cane Manufacturing Inc., 28 USPQ2d 1457, 1477 (E.D. La. 1993); emphasis added.][4]

4. "[T]here is a close relationship between the enablement aspect of section 112 and the utility requirement of section 101." [Phillips Petroleum Co. v. U.S. Steel Corp., 6 USPQ2d 1065, 1102 (D. Del. 1987), *aff'd* 9 USPQ2d 1461 (Fed. Cir. 1989).]

The Patil et al. article cited in the Office Action not only does not cast doubt on the statements relied upon for enabling support of the claimed invention, but in itself supports the "objective truth" of such statements, supports enablement for the small degree of utility required in accordance with patent law principles. Applicants respectfully submit that the PTO's burden has not been met in this case, that the presumptively correct disclosure stands, and that the burden has not shifted to the Applicants to provide rebuttal evidence.

According to MPEP § 2164.02, an in vitro working example should be accepted as correlating with in vivo methods, unless the examiner has evidence that it does not. However, the Examiner has not provided a fact-based explanation that focuses on the claimed methods, as opposed to antisense therapy as a general field, to explain that the instant claims are not enabled.

Applicants respectfully conclude that even if the PTO had met the burden of proof to challenge the presumptively enabling disclosure of the specification, that the evidence presented above, notably the Declaration of Dr. Gruenert (Appendix I), would be sufficient to rebut any inference that ones of skill in the art would reasonably doubt the statements relied upon for enabling support in the specification. The references provided describing the *in vivo* efficacy of

structurally similar antisense nucleic acid sequences support Dr. Gruenert's Declaration which is based not only on prior art in vivo studies, but also in the factual evidence provided by the MN experiments reported in the Specification.

As explained in detail above, the support provided in the Specification and the articles incorporated by references, combined with conventional knowledge in the art, provide the degree of enablement required for patentability. Applicants respectfully request that the Examiner reconsider the instant 35 USC § 112, first paragraph rejection in view of the above remarks, and withdraw this rejection.

CONCLUSION

Applicants respectfully conclude that Claims 39 and 40 are in condition for allowance, and that since Claims 31-35 and 53-55 have already been found in condition for allowance (Office Action, top of page 6) earnestly request that all the claims be promptly allowed. If for any reason the Examiner feels that a telephone conference would expedite the prosecution of the

subject application, the Examiner is invited to telephone the undersigned Attorney for Applicants at (415) 981-2034.

Respectfully submitted,

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